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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/764,428	SIMMONS, LAURA	
	Examiner	Art Unit	
	PHUONG HUYNH	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1-25, 28-34, 36-61, 63-74, 96-114, 116-1*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25,28-34,36-61,63-74,96-114,116-127,129 and 130* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25, 28-31,33-34, 36-37 and 71-73* is/are rejected.

7)☒ Claim(s) *1-25,28-34,36-61,63-74,96-114,116-127,129 and 130* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/31/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-25, 28-34, 36-61, 63-74, 96-114, 116-127, 129 and 130 are pending.

2. The previous objection and rejections are hereby withdrawn in view of the amendment to the claims filed December 11, 2007.

3. New ground of objection and rejections are set forth below.

4. Claims 1-25, 28-34, 36-61, 63-74, 96-114, 116-127, 129 and 130 are objected to because the fonts are too small, crowded too closely together, making reading difficult. Substitute claims with font (*e.g.*, Arial, Times Roman, or Courier, preferably a font size of 12), lines one and one-half or double spaced on good quality paper are required. See 37 CFR 1.52 (b). Because of the fonts are too small combined with the poor quality of the FAX, some letter and punctuation marks are illegible. For example, "IIVR2" in claim 71, line 11, should have been "**H**VR2". The letter "c" and "e" cannot be distinguishable; the punctuation mark "." and "," cannot be distinguishable.

5. Claims 63 and 64 are objected to because "**a** anti-VEGF antibody" should have been "**an** anti-VEGF antibody".

6. Claim 130 is objected to because of the typographical error "at the at least".

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

8. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

9. Claims 25, 29, 31, 33-34, 36 and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 5,693,762 B1 (newly cited issued Dec 2, 1997; PTO 892).

The '762 patent teaches a method of producing humanized antibody or antigen binding fragment thereof comprising the steps of (1) aligning the sequence of donor non-human immunoglobulin heavy or light chain variable region with a subgroup sequences of human heavy chain or light chain variable regions or consensus sequence or subgroups of sequences (see claim 14 step 1, claim 16 step 1 of the '762, summary of invention, col. 13, lines 8-10, col. 14, line 16-20, in particular), (2) selecting the human acceptor heavy and light chain variable regions that is most homologous (most identity) to the heavy and light chain variable regions of the donor immunoglobulin (see col. 13, lines 14-17, claim 14, step 2, claim 16, step 2 of the '762 patent, col. 13, line 47-50, col. 16, line 5, in particular) and (3) preparing vector comprising the sequence encoding the humanized antibody and expressing recombinant DNA encoding the heavy and light chain CDRs from a donor immunoglobulin and human framework regions from the consensus sequence in host cell such prokaryotic host cells or mammalian host cells such as CHO cell (see col. 17 lines 62 through col. 18, lines 1-48, col. 40, line 20-21, claims 14 and 16, steps 3-5, claim 20, in particular). Claim 29 is included in this rejection because reference framework regions inherently encompasses all FR1, FR2, FR3 and FR4 (see claim 20 of the '762 patent, in particular). Claims 33 and 34 are included in this rejection because the term "comprising" is open ended. It expands the variable domain to include the heavy chain variable region 1, 2, and 3 from the non-human immunoglobulin heavy chain and the selected frameworks from the human consensus subgroup sequence. Thus the reference teachings anticipate the claimed invention.

10. Claims 25, 29, 31, 33-34, 36-37, and 71-73 are rejected under 35 U.S.C. 102(b) as being anticipated by Kolbinger et al (newly cited, Protein Engineering 6(8): 971-980, 1993; PTO 892).

Kolbinger et al teach a method of preparing humanized antibody comprising the steps of (1) aligning the sequence of donor non-human immunoglobulin heavy or light chain variable region such as C21 with a subgroup consensus sequence of human heavy chain such as SGI or light chain variable regions subgroup consensus sequence such as SGIII (see entire document, Figures 2 and 3, in particular), and selecting the subgroup consensus sequence such as SGI for heavy chain (see Figure 3, in particular) and SGIII for light chain (see Figure 2, in particular), (2) selecting the amino acid found in the corresponding position of the human subgroup variable domain sequence with the most identity with the corresponding HVR1 and VHR2 amino acid and (3) substituting at least one amino acid proximal to a cys residue that partipates in an intrachain variable domain disulfide bond with a different amino acid such as X for K at position 19 (see sequences H1 and H3 of Fig 3, in particular). (4) expressing the humanized antibody such as human C21 (see page 973, col. 1, in particular) and recovering the humanized antibody from host cell such as COS cell (see page 973, Protein A purification, in particular). Thus the reference teachings anticipate the claimed invention.

11. Claims 25 and 29-31 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 5,558,564 (newly cited, issued Sept 1996; PTO 892).

The '564 patent teaches a process for the preparation of a humanized monoclonal antibody, comprising hypervariable regions (CDRs) of antigen-binding sites of non-human origin, and FRs of variable regions and constant regions of the light and heavy chains of human origin by cultivating transformed host cells in a culture medium and purifying and isolating the expressed antibody proteins (see col. 9, lines 34, in particular). The reference method comprises the steps of aligning V.sub.L and V.sub.H genes for MAb 425 are shown in FIG. 2. The amino acid sequence of the 425 V.sub.L and V.sub.H regions, are compared to other mouse variable regions in the Kabat data base (Kabat et al., 1987). The V.sub.L region can be classified into the mouse kappa chain variable region subgroup IV or VI. Within the FRs, the 425 V.sub.L region has an approximately 86% identity to the consensus sequence for mouse kappa subgroup IV and an approximately 89% identity to subgroup VI. The 425 V.sub.L region appear to use the JK4 segment. Examination of the VH region shows an approximately 98% identity to the FRs of the consensus sequence for mouse heavy chain subgroup II (B) (see col. 14, lines 1-22, in particular),

select the human FRs on which to graft the mouse CDRs, the FRs of mouse MAb 425 V.sub.H region are compared with the FRs from the consensus sequences for all subgroups of human V.sub.H regions (Kabat et al., 1987). This comparison shows that the FRs of mouse MAb 425 V.sub.H are most like the FRs of human V.sub.H subgroup I showing an approximately 73% identity within the FRs and an approximately 65% identity over the entire V.sub.H regions (see col. 16, lines 29-61, in particular). The method than constructs one or several expression vectors comprising in each case at least a promoter, a replication origin and the coding DNA sequences encoding for the light and heavy chains can be present together in one or, alternatively, in two or more different vectors, and finally, transforming the host cells with one or more of the expression vectors in host cell such as COS cells (see col. 15, lines 55-65, in particular). The reference human subgroup variable domain consensus sequence comprises a heavy chain domain FR1 sequence of SEQ ID NO: 11, which is 100% identical to the claimed SEQ ID NO: 1 (see reference SEQ ID NO: 11, col. 9, lines 13, in particular). Thus the reference teachings anticipate the claimed invention.

12. Claims 25, 28, 29, 31, 33-34, 36 and 37 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No 6,884,879 (of record, filed August 6, 1997; PTO 892) as evidenced by US Pat No 5,693,762 B1 (newly cited issued Dec 2, 1997; PTO 892).

The '879 patent teaches a method of preparing a humanized antibody or antigen binding fragment thereof wherein said antibody or antigen binding fragment thereof that binds to VEGF and has the HVR1 amino acid sequence of GYTFTYGIN (reference SEQ ID NO: 110) or GYDFTHYGMN (reference SEQ ID NO: 128) which are 100% identical to the claimed SEQ ID NO: 14 and SEQ ID NO: 18, respectively. The reference method for preparing humanized anti-VEGF antibody or antigen binding thereof by expressing said antibody having or antigen binding fragment thereof in host cell such as prokaryote *E coli* or mammalian host cell such as VERO or CHO cell (see col. 25 lines 126 through col. 26, in particular) and recovering said antibody or antigen binding fragment thereof (see col. 27, lines 35-61, in particular). The reference variable heavy chain framework (FR) sequence of the non-human monoclonal antibody has amino acids substitution from the human consensus sequence subgroup III (see col. 14, lines 34-67 through col. 15, lines 1-2, sequence alignment in Figure 1A, in particular). The reference variable light chain framework (FR) sequence of the non-human monoclonal antibody has amino acids substitution from the human consensus sequence subgroup I (see col. 15, lines 28-44, sequence

alignment in Figure 1B, in particular). Although claim 25 has been amended to include the step of aligning the mouse and human HVR1 and HVR2 domains, it is known in the art as evidenced by the '762 patent that method of preparing humanized antibody begins with the step of aligning the aligning the sequence of donor non-human immunoglobulin heavy or light chain variable region with a subgroup sequences of human heavy chain or light chain variable regions or consensus sequence or subgroups of sequences (see claim 14 step 1, claim 16 step 1 of the '762, summary of invention, col. 13, lines 8-10, col. 14, line 16-20, in particular), (2) selecting the human acceptor heavy and light chain variable regions that is most homologous (most identity) to the heavy and light chain variable regions of the donor immunoglobulin (see col. 13, lines 14-17, claim 14, step 2, claim 16, step 2 of the '762 patent, col. 13, line 47-50, col. 16, line 5, in particular). As such, the method of humanized anti-VEGF antibody as taught by the '879 patent inherently has the initial step of aligning the sequence of donor non-human immunoglobulin heavy or light chain variable region with a subgroup sequences of human heavy chain or light chain variable regions or consensus sequence or subgroups of sequences. Thus the reference teachings anticipate the claimed invention.

13. Claims 25-31, 33, 36-37 and 71-73 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 98/45331 publication (of record, published Oct 1998; PTO 1449) as evidenced by US Pat No 5,693,762 B1 (newly cited issued Dec 2, 1997; PTO 892).

The WO 98/45331 publication teaches a method for preparing humanized antibody or antigen binding fragment thereof by expressing the humanized antibody or antigen binding fragment comprising the variable domain in host cell and recovering the reference humanized antibody (see entire document, abstract, page 25-26, page 37, in particular). The reference furthers the antibody variable domain cysteine residues not involved in maintaining the proper conformation of the humanized or variants thereof may also be substituted to improve oxidative stability and prevent aberrant crosslinking, see page 28, in particular). The reference method for preparing humanized anti-VEGF antibody or antigen binding thereof by expressing said antibody having or antigen binding fragment thereof in host cell such as prokaryote *E coli* or mammalian host cell such as VERO or CHO cell (see page 37, in particular) and recovering said antibody or antigen binding fragment thereof (see col. 38, in particular). The reference variable heavy chain framework (FR) sequence of the non-human monoclonal antibody has amino acids substitution from the human consensus sequence subgroup III (see page 61, in particular). The reference

variable light chain framework (FR) sequence of the non-human monoclonal antibody has amino acids substitution from the human consensus sequence subgroup I (see page 61-63 in particular). The reference humanized antibody or antigen binding fragment thereof wherein said antibody or antigen binding fragment thereof has the GYDFTHYGMN (see page 74, Y0243-1, reference SEQ ID NO: 86) which is identical to the claimed SEQ ID NO: 18. Although claim 25 has been amended to include the step of aligning the mouse and human HVR1 and HVR2 domains, it is known in the art as evidenced by the '762 patent that method of preparing humanized antibody begins with the step of aligning the aligning the sequence of donor non-human immunoglobulin heavy or light chain variable region with a subgroup sequences of human heavy chain or light chain variable regions or consensus sequence or subgroups of sequences (see claim 14 step 1, claim 16 step 1 of the '762, summary of invention, col. 13, lines 8-10, col. 14, line 16-20, in particular), (2) selecting the human acceptor heavy and light chain variable regions that is most homologous (most identity) to the heavy and light chain variable regions of the donor immunoglobulin (see col. 13, lines 14-17, claim 14, step 2, claim 16, step 2 of the '762 patent, col. 13, line 47-50, col. 16, line 5, in particular). As such, the method of humanized anti-VEGF antibody as taught by the WO publication inherently has the initial step of aligning the sequence of donor non-human immunoglobulin heavy or light chain variable region with a subgroup sequences of human heavy chain or light chain variable regions or consensus sequence or subgroups of sequences (acceptor sequence). Thus the reference teachings anticipate the claimed invention.

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B O'Hara can be reached on (571) 272-0878. The IFW official Fax number is (571) 273-8300.

16. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/
Primary Examiner, Art Unit 1644
March 14, 2008